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Staying hepatitis C negative: a systematic review and meta-analysis of cure and reinfection in people who inject drugs

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LIST OF ABBREVIATIONS (in order of appearance)

DAAs	direct acting antivirals
PWID	people who inject drugs
SVR	sustained viral response
OST	opioid substitution therapy
CI	confidence interval
HCV	hepatitis C virus
EASL	European Association for the Study of the Liver
AASLD	American Association for the Study of the Liver
INHSU	International Network on Hepatitis in Substance Users
AU	Australia
RNA	ribonucleic acid
NOS	Newcastle-Ottawa Scale
ITT	intention-to-treat analysis
mITT	modified-intention-to-treat- analysis

DOT

directly observed therapy

CONFLICT OF INTEREST STATMENT

Joseph Doyle receives funding from Abbvie, Gilead Sciences, Bristol Myers Squibb and Merck for investigator initiated research grants, and consultancy from Abbvie, Gilead Sciences, Bristol Myers Squibb and Merck. Alisa Pedrana receives funding from Merck for investigator initiated research grants. Sharon Hutchinson receives honoraria from Gilead Sciences. Margaret Hellard receives funding from Gilead Sciences Abbvie and GSK for investigator initiated research. All other authors declare no potential conflicts of interest.

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STATEMENT OF AUTHOR CONTRIBUTIONS

Rachel Sacks-Davis, Margaret Hellard, Joseph Doyle, Alisa Pedrana, Paul Agius, Esther Aspinall, Sharon Hutchinson and Ned Latham contributed to study conception and design. Ned Latham, Anna Palmer, Joost Vanhommerig, Stelliana Goutzamanis, Zinia Li, Magnus Gottfredsson, Julie Bouscaillou, Alyona Mazhnaya, Frederick Altice, Sahar Saeed, Marina Klein, Oluwaseun Falade-Nwulia and Niklas Luhmann contributed to the acquisition of data. All authors contributed to the analysis and interpretation of data; drafting of the manuscript and critical revision of the manuscript for important intellectual content. Rachel Sacks-Davis, Paul Agius, Joseph Doyle, Margaret Hellard and Ned Latham contributed to the statistical

analysis. Margaret Hellard obtained funding, Rachel Sacks-Davis and Margaret Hellard contributed to study supervision.

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ABSTRACT

Background and Aims

Direct-acting antivirals (DAAs) are highly effective in treating hepatitis C. However, there is concern that cure rates may be lower, and reinfection rates higher, amongst people who inject drugs. We conducted a systematic review of treatment outcomes achieved with DAAs in PWID.

Methods

A search strategy was used to identify studies that reported sustained viral response (SVR), treatment discontinuation, adherence or reinfection in recent PWID and/or opioid substitution therapy (OST) recipients. Study quality was assessed using the Newcastle-Ottawa Scale. Meta-analysis of proportions was used to estimate pooled SVR and treatment discontinuation rates. The pooled relative risk of achieving SVR was also calculated using a generalised mixed-effects linear model.

Results

The search identified 8075 references; 26 were eligible for inclusion. The pooled SVR for recent PWID was 88% (95% CI, 83% – 92%) and 91% (95% CI 88% – 95%) for OST recipients. The relative risk of achieving SVR for recent PWID compared to non-recent PWID was 0.99 (95% CI, 0.94 – 1.06). The pooled treatment discontinuation was 2% (95% CI, 1% – 4%) for both recent PWID and OST recipients. Amongst recent PWID the pooled incidence of reinfection was 1.94 per 100 person years (95% CI, 0.87 – 4.32). In OST recipients, the incidence of reinfection was 0.55 per 100 person years (95% CI, 0.17 – 1.76).

Conclusions

Treatment outcomes were similar in recent PWID compared to non-PWID treated with direct-acting antivirals. People that report recent injecting or OST recipients should not be excluded from hepatitis C treatment.

Abstract

KEY POINTS

- People who inject drugs are currently excluded from hepatitis C treatment by jurisdictions and individual practitioners, partially based on concerns regarding efficacy and reinfection risk
- We identified 26 studies which reported treatment outcomes or people who inject drugs and/or people receiving opioid substitution therapy, including cure and reinfection.
- People who inject drugs, as well as OST recipients, both achieved high rates of hepatitis C cure
- The risk of reinfection after treatment was relatively low, however was limited by the short follow up periods in published studies

BACKGROUND

Hepatitis C (HCV) is a blood-borne virus, which in high-income countries is primarily transmitted amongst people who inject drugs (PWID).^{1,2} Curing HCV reduces mortality and improves quality of life.^{3,4} Treating PWID also reduces the risk of transmission, and is an essential component of achieving the World Health Organization HCV elimination targets.⁵ Despite recommendations that PWID receive treatment,⁶⁻⁸ this population continues to be excluded; both by individual practitioners,⁹ and at a systemic level.^{10,11}

Our 2013 systematic review of interferon/ribavirin therapy found that PWID receiving treatment had high levels of adherence (82%, 95% CI 74% - 89%), low treatment discontinuation (22%, 95% CI 16% - 27%), and similar SVR rates (56%, 95% CI 50% - 61%) to non-PWID in real-world settings.¹² A systematic review of treatment outcomes in people reporting recent drug use, including a subgroup of people who inject drugs, found that this population achieves relatively high rates of cure with DAAs.¹³ Despite the effectiveness of DAAs, concerns about reinfection in PWID have been raised and may partially account for practitioner unwillingness to prescribe DAA therapy to this population.⁹

Low rates of reinfection were observed among those PWID treated with interferon-based therapies,^{12,14} but this may be different in the DAA era. Indeed, given that DAA treatments are significantly more effective and tolerable than interferon-based therapies, it is possible that the availability of DAA treatment may result in an increase in the number of people with ongoing risk behaviour who achieve cure, and in turn increase the total population at risk of reinfection.

Several studies have investigated DAA therapy outcomes amongst PWID, including reinfection, but the number of recent PWID included in each study is small (range: 23 – 163).¹⁵⁻²⁷ We conducted a systematic review and meta-analysis to measure SVR, treatment discontinuation, adherence, and reinfection amongst recent PWID and OST recipients treated with DAAs.

METHODS

Study identification

In November 2017, a search strategy (see Supplementary Material) was used to identify relevant English-language studies in MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Search results were limited to the year 2010 and onward. Proceedings from The International Liver Congress (EASL), The Liver Meeting (AASLD), and the International Symposium on Hepatitis Care in Substance Users (INHSU) from 2015 to 2017 were also searched. The review protocol was prospectively registered with PROSPERO (CRD42017083604).

Study selection

Search results were uploaded to Covidence (Melbourne, AU) and independently assessed by two reviewers using pre-specified criteria (Table 1). Authors of studies that included, but did not report outcomes for, recent PWID were contacted for additional data. Studies that reported SVR, reinfection, treatment discontinuation and/or adherence in recent PWID and/or people receiving OST were eligible for inclusion in the meta-analysis.

Data extraction

Data were extracted independently by two reviewers using a standardized spreadsheet. Where a study resulted in multiple publications, the most up-to-date data available was used. The following data were extracted:

Study and participant characteristics

Country, setting, study design, number of study sites, treatment regimen, adherence intervention, inclusion and exclusion criteria, definition(s) of recent PWID, number of OST recipients, previous substance use, age, gender, genotype and cirrhosis were extracted.

Primary outcome

The primary outcome was SVR, defined as undetectable HCV RNA at least 12 weeks after treatment completion. SVR was extracted on an intention-to-treat, modified intention-to-treat (participants that were missing SVR test results, but had attained undetectable HCV RNA at end of treatment were assumed to be cured) and/or according to study definitions.

Secondary outcomes

The definition of adherence and the number of participants meeting this definition were extracted. Treatment discontinuation was defined as the number of participants that commenced, but did not complete therapy, including those that died during treatment. Reinfection was defined as detectable HCV RNA after SVR, or after treatment completion in combination with a change in genotype or viral sequence

Risk of bias

The Newcastle-Ottawa Scale (NOS),²⁸ was used to assess the quality of included studies. Each study was independently scored from zero (low quality) to nine (high quality) by two reviewers. Studies without a comparison group were assessed using a modified scale (score out of six). Sensitivity analyses were conducted excluding studies scoring ≤ 6 (out of 9) or ≤ 4 (out of 6) on the relevant scale. A funnel plot was used to assess publication bias.

Data synthesis and analysis

All statistical analyses were performed using Stata 15 (StataCorp, College Station, USA).

Random-effects meta-analysis of proportions was used to estimate the pooled SVR in recent PWID and OST recipients using the Stata metaprop_one package.²⁹ Standard errors were calculated using the Wilson method. The Freeman-Tukey arcsine transformation was used for studies where all patients achieved SVR.

Pooled relative risks of achieving SVR in recent PWID and OST recipients (compared to non-recent PWID or non-OST recipients, respectively) were calculated using DerSimonian and Laird random-effects models (for $I^2=25-75\%$) or Mantel and Haenszel fixed-effects models (for $I^2<25\%$) using the Stata metan package.^{30,31}

SVR was calculated on an intention-to-treat (ITT) and modified intention-to-treat (mITT)/other basis. To be included in the ITT analysis, a study was required to report the total number of people (recent PWID and/or OST recipients) that commenced treatment.

SVR in recent PWID and OST recipients

The relative risk of achieving SVR in recent PWID and OST recipients (compared to non-recent PWID or non-OST recipients, respectively) was calculated. In studies where all participants met the primary definition of recent PWID, the secondary definition was used in the relative risk calculation. A constant continuity correction (0.5) was used for meta-analysis of relative risk.³²

Post-treatment reinfection in recent PWID and OST recipients

The pooled reinfection rate was calculated using a generalised mixed-effects linear model with a poisson family, log link function and a random effect for study.

Secondary outcomes

Meta-analysis of proportions was used to estimate the pooled proportion discontinuing treatment in recent PWID and OST recipients.

Studies where all patients achieved SVR

In studies where all patients achieved SVR, the Freeman-Tukey double arcsine transformation was used for meta-analysis of proportions and a constant continuity correction (0.5) was used for meta-analysis of relative risk.³²

Additional analyses

Pre-specified subgroup and sensitivity analyses were performed examining the effect of country (high- vs. middle- income), setting (real-world vs. clinical trial), recent PWID definition, adherence intervention (any vs. none), and study quality (all studies vs. high-quality studies only) on SVR. Sensitivity analyses were also performed without data

transformations or continuity corrections, and with an alternative continuity correction (the reciprocal of the opposite group arm size).³³

RESULTS

The search yielded 8075 studies, of which 155 were eligible for full-text review (Figure 1). Of the 26 included studies, 14 reported outcomes for recent PWID and 19 reported outcomes for OST recipients.

Study characteristics

Studies reporting SVR

Thirteen studies reported SVR in recent PWID, of which the majority (n=10) were real-world studies conducted in high-income countries. Recent PWID were most commonly defined as people reporting injecting in the past 6 months (n=5). Other definitions were injecting: during treatment (n=2); in the past year (n=2); the past month (n=2). The remaining two studies defined recent PWID as people attending a needle syringe program at the time of recruitment (n=1), or in the past year (n=1). Seven studies provided adherence support services. Two offered directly observed therapy (DOT); one of which required all participants to receive daily DOT.

Nineteen studies reported SVR in OST recipients. The characteristics of these studies are summarised in Table 2. The vast majority (n=18) were conducted in high-income countries; eight of which were clinical trials. Seven studies, provided adherence support; including daily DOT for all participants (n=3), dispensing medication at a needle syringe program (n=1), and case management (n=3).

Studies reporting adherence and discontinuation

Six studies (Table 4) reported adherence, five of which were clinical trials. Most (n=5) reported adherence in OST recipients; only two reported adherence for recent PWID.^{27,34} Adherence was most commonly defined as the percentage of doses taken and ranged from $\geq 80\%$ (n=1),³⁵ $\geq 90\%$ (n=3),^{34,36,37} and $>95\%$ (n=1).³⁸ The remaining study provided participants with daily DOT, and noted that no participants missed more than one dose.²⁷ In studies that did not provide adherence support, adherence was assessed by pill count (n=3),³⁵⁻³⁷ a participant-completed electronic medication diary (n=1),³⁸ or an electronic blister pack (n=1).³⁴ Fifteen studies reported treatment discontinuation: in recent PWID (n=5),^{17,19,22,27,34} or OST recipients (n=10).^{22,27,35-37,39-43} Reasons for discontinuation included death, incarceration, and loss to follow-up.

Studies reporting reinfection

Nine studies (Table 3) reported reinfection data; six for recent PWID and four for OST recipients. The follow-up period during which reinfection could be detected ranged from 24 weeks to three years after treatment completion. Early reinfection was distinguished from treatment failure by comparison of genotype/subtype and/or viral sequencing.

Risk of bias

The mode NOS score was seven out of nine (range 5 – 9) for studies that included a comparison group (n=14). Amongst studies without comparison groups (n=12) the mode NOS score was five out of six (range 4 – 6). In total 16 studies, were deemed to be of high quality (NOS ≥ 7 or modified NOS ≥ 5). In studies with comparison groups, the most common source of potential bias was a possible difference between the recent PWID or OST group and the comparison group in terms of cirrhosis or other baseline factors such as age or

genotype.^{15,20,22,24-27,36,37,40,44-46} This was either due to lack of reporting of baseline characteristics by recent PWID or OST group, or reporting of a statistically significant difference between groups. Ten studies were also deemed to be at high risk of bias in terms of the representativeness of the recent PWID or OST group.^{27,35-38,40-42,47,48} The most common (n=6) potential source of bias in this domain was the requirement that participants be on 'stable OST'.^{27,35,37,38,41,42} Seven of the nine studies that reported reinfection followed participants for less than one year after treatment completion and were thus deemed to be at high risk of bias for this outcome. There was no evidence of publication bias for the relative risk of SVR in recent PWID and OST recipients (Supplementary Figure).

Synthesis of results

Pooled SVR in recent PWID

SVR data was presented for recent PWID across 13 studies. Amongst the ITT population (n=827) the pooled SVR was 88% (95% CI 83% – 92%; Figure 2a). There was substantial heterogeneity ($I^2 = 74\%$), which persisted when the analysis was limited to real-world studies conducted in high-income countries ($I^2 = 68\%$). In the mITT/as-defined analysis, 10 studies of 665 recent PWID were included. The pooled SVR in recent PWID was 91% (95% CI: 86% – 95%; Figure 2b) with considerable heterogeneity ($I^2=75\%$).

Pooled SVR in OST recipients

Nineteen studies presented SVR data for OST recipients. In the ITT population (n=1086) the pooled SVR was 91% (95% CI 87% – 95%; Figure 2c). There was substantial heterogeneity ($I^2=72\%$), which persisted when the analysis was limited to real-world studies in high-income countries ($I^2=72\%$). The substantial heterogeneity observed within these real-world studies

can be largely attributed to one study,²⁷ which had a markedly different methodology (intensive case management) and yielded an SVR of 100%. Limiting the analysis to clinical trials yielded a pooled SVR of 94% (95% CI, 92% – 96%) with minimal heterogeneity ($I^2=15\%$). In the mITT/as-defined analysis (Figure 2d) the pooled SVR was 98% (95% CI, 94% - 100%) with substantial heterogeneity ($I^2=63\%$).

Relative risk of achieving SVR in recent PWID

Compared to people not reporting recent injecting, the pooled relative risk of achieving SVR in recent PWID was 0.99 (95% CI, 0.93 – 1.05, $p=0.67$; Figure 3a) in the ITT population and 0.94 (95% CI, 0.89 – 0.99, $p=0.01$) in the mITT/as-defined population. Moderate heterogeneity ($I^2=36\%$) was observed in the ITT analysis but not the mITT/as-defined analysis ($I^2=15\%$).

Relative risk of achieving SVR in OST recipients

Compared to non-OST recipients, the pooled relative risk of achieving SVR in OST recipients was 0.97 (95% CI, 0.95 – 0.997, $p=0.03$; Figure 3b) in the ITT population and 1.00 (95% CI, 0.97 – 1.03, $p=0.98$) in the mITT/as-defined population. No heterogeneity was observed in these analyses ($I^2=0\%$).

Treatment discontinuation

Five studies (Supplementary Table) reported treatment discontinuation in recent PWID. Amongst recent PWID ($n=342$) the pooled discontinuation was 2% (95% CI, 1% – 4%). No heterogeneity was observed ($I^2=0\%$). The pooled estimate was identical for the nine studies that reported discontinuation in OST recipients ($n=570$). There were insufficient studies with comparison groups to determine the relative risk of discontinuation.

Adherence

There were insufficient primary data (n=2) on adherence to derive pooled estimates for recent PWID. Adherence is summarised in Table 4.

Reinfection

Amongst people reporting recent injecting, the pooled incidence of reinfection was 1.94 per 100 person years (95% CI, 0.87 – 4.32). In OST recipients, the incidence of reinfection was 0.55 per 100 person years (95% CI, 0.17 – 1.76).

Sensitivity analyses

None of the results were sensitive to exclusion of low quality studies, exclusion of studies that did not define recent PWID as injection within a specified timeframe prior to treatment initiation, use or modification of the continuity correction, or use of the Freeman-Tuckey arcsine transformation.

DISCUSSION

Recent PWID and OST recipients achieve high rates of SVR when treated with DAAs (88% and 91%, respectively). The SVR rate was at least 75% for recent PWID in all but one small study conducted in a lower-middle-income country (n=25; SVR=64%).²² Importantly, when recent PWID were compared to people not reporting recent injecting, there was no clinically significant difference in SVR attainment (RR 0.99; 95% CI, 0.93 – 1.05). This was also true for people receiving OST during treatment (RR 0.97; 95% CI, 0.95 - 1). Our review highlights that routinely excluding recent PWID from treatment is not supported by evidence and prevents people who are likely to achieve cure from doing so.

Treatment discontinuation was very low amongst recent PWID and OST recipients (approximately 2% in both groups) highlighting the high tolerability of DAA regimens and the capacity of recent PWID and OST recipients to complete treatment. Of the few studies that reported various definitions of adherence, the number of participants deemed to be adherent was almost always greater than 90%. In the one study of recent PWID in which adherence was relatively low (66%) the vast majority of participants (94%) still achieved SVR.³⁴ This is consistent with other real-world studies that did not meet the inclusion criteria for this review but reported adherence in cohorts with large proportions of recent PWID or OST recipients. A study of 61 patients (95% OST recipients) found that 41% took at least 80% of doses on the correct day (measured by an electronic blister pack).⁴⁹ A study of 23 participants receiving directly observed therapy (93% recent PWID, 85% OST recipients) found that 48% received >90% of doses on the correct day.⁵⁰ In both studies, missed doses were made up at a later date, and preliminary SVR results were high. A third study conducted in alcohol and other drug clinics (50% recent PWID, 38% OST recipients) reported 93% adherence but this was measured by self-report.²⁴ More primary data is required to characterise the relationship between adherence and SVR in recent PWID and OST recipients, but the available evidence suggests that even in the context of low adherence, high SVR rates are achievable.

Our review found low pooled rates of HCV reinfection. While this is encouraging, it is important to note that the observation period for reinfection in most of the included primary studies was relatively short. At the very least, our results suggest that the vast majority of recent PWID remain free from reinfection for at least 24 weeks following the end of treatment. The length of follow up after HCV treatment in primary studies of recent PWID is likely to increase over time, with expanding access to DAAs and the completion of planned

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follow-up periods for established studies. In the interim, it is encouraging that low rates of reinfection were observed in the small number of currently available studies with longer follow-up periods.^{18,51,52}

Even if subsequent studies with longer follow-up periods and a greater number and diversity of PWID and OST recipients demonstrate lower rates of SVR or a higher rate of reinfection, it is essential that these groups not be excluded from treatment. Indeed, that an individual who achieves an EoTR or SVR subsequently becomes reinfected highlights that the initial treatment reached an individual at high risk of not only acquiring, but also transmitting, hepatitis C – a population that is essential to treat to achieve the WHO elimination goals.⁵ To this end, instead of attempting to reduce reinfection by precluding those with risk factors from treatment, reinfection should be proactively prevented: through education to treatment recipients with risk factors and providing consistent access to harm reduction services including syringe services and medication assisted treatment during and after treatment. After completing treatment, individuals at risk for reinfection should remain under surveillance for reinfection and be promptly re-treated.

A key strength of our review is that it is the first of which we are aware to quantitatively synthesise data for reinfection after treatment with DAAs for recent PWID and OST recipients. In addition by systematically contacting authors where necessary to obtain outcome data by injecting behaviour, our review expands the currently available body of evidence and is the largest review of SVR in recent PWID (n=827 in the ITT analysis). Synthesising the results of these studies is particularly important given that the majority of published studies contain fewer than 100 recent PWID or OST recipients

Despite these strengths, our review also had a number of limitations. Classification of recent PWID varied between studies so the categorisation used in this review included a broad spectrum of injecting behaviour: from injecting during treatment to injecting in the 12 months prior to treatment. The analysis of reinfection risk is also limited by the length of the follow up periods in the primary studies. It is also possible that the selection processes of the individual studies favoured people that were already relatively well engaged in healthcare and who may have relatively better treatment outcomes, including lower rates of reinfection. The extent to which this occurred is not apparent as most studies did not report indicators of social stability including housing and employment. While most studies did report other baseline characteristics such as genotype and cirrhosis, very few studies reported these characteristics by the sub-groups of interest (recent PWID, OST recipients). As such, it was not possible to perform a meta-regression of SVR for either of the populations included in our review.

Our review highlights that recent PWID treated with DAAs consistently complete treatment, obtain high rates of SVR and largely avoid early reinfection. There was no clinically significant difference between recent PWID and OST recipients compared to other patients. These findings are particularly important because despite recommendations from EASL and AASLD to the contrary, PWID continue to be excluded from treatment.^{10,11,53}

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Table 1: Eligibility criteria

Population	Recent PWID, primarily defined as people who reported injecting drugs within the year prior to treatment for chronic hepatitis C <i>and/or</i> People receiving opioid substitution therapy (OST) at the time of treatment for chronic hepatitis C Studies where the above group(s) only comprised a proportion of all study participants were eligible provided: that there were at least 15 participants in either of the above group(s); and that the outcome(s) of interest were reported for this/these group(s) Participants treated in a custodial setting were excluded
Intervention	Treatment with any interferon-free direct-acting antiviral regimen. Studies which included a combination of interferon-free and interferon-containing regimens were eligible provided that population and outcome data were reported in the study for the interferon-free group (or if this information was made available by the authors)
Comparison	No comparison group <i>or</i> The same intervention in non-recent PWID or people not receiving OST
Outcome	SVR (undetectable hepatitis C RNA at least 12 weeks after treatment completion) <i>and/or</i> Treatment adherence (completion of treatment as planned) <i>and/or</i> Treatment discontinuation <i>and/or</i> Reinfection
Study type	Prospective or retrospective, interventional or observational studies

Table 2: Characteristics of included studies

Author Year Location	Study type (# of sites if spec.)	1° def. recent PWID (% of cohort)	2° def. recent PWID (% of cohort)	Cirr- hosis (%)	OST (%)	Hepatitis C treatment regimen	Treat-ment Setting	Adherence intervention	Comparison group(s)
Bielen 2017 Belgium ¹⁵	RC (15)	Injecting during treatment (3)	-	59	9	PrOD SOF/DCV SOF/SMV	Hospital- based	None	1° definition compared to all other participants
Boglione 2017 Italy ¹⁶	PC (1)	Injecting within the past year (100)	-	67	34	PrOD+RBV SOF/DCV± RBV SOF/LDV SOF/RBV SOF/SMV± RBV	Hospital- based	None	-
Bouscaill- ou* 2017 Georgia ¹⁷	RC (1)	Attending an NSP within the past year (100)	Injecting during treatment (44)	NR	NR	SOF/LDV SOF+RBV	Comm. clinic/harm reduction centre	Peer support & on-site peer navigation	The 2° definition subgroup was compared to all other participants
Boyle 2017 Scotland ³⁹	RC	-	-	16	100	PrOD±RBV PrO+RBV	Community pharmacy providing directly- observed OST	Twice daily DAA dosing; first dose observed with OST, second dose provided to take-away	None
Conway 2016 Canada ¹⁸	RC (1)	Ongoing injecting (100)	-	26	40	PrOD±RBV SOF+RBV SOF/LDV ±RBV	Community- based infectious diseases clinic	Multidisciplinary approach addressing medical, psychiatric, social and addiction- related need	-
Conway 2017 Multi- country	Clinical trial	Injecting within the previous month (45)	-	8	72	PrOD±RBV	Clinical trial; treatment in community or hospital clinics	None	1° definition compared to all other participants
Dore 2016 Multi- country	RCT	-	-	21	100	EBR/GRZ	Clinical trial	None	None
Eckhardt 2018 USA ¹⁹	PC (1)	NSP attendees (100)	Injecting within the past month (85)	NR	45	EBR/GRZ PrOD+RBV SOF/LDV SOF+RBV SOF/SMV SOF/VEL	Onsite treatment at a needle syringe program	Care co- ordination; DAA dispensed at NSP on daily, weekly or monthly basis	2° definition compared to all other participants; OST participants compared to non-OST recipients attending NSP
Gottfreds- son* 2017 Iceland ²⁰	PC (>1)	Injecting within the past 6 months (33)	Injecting within the past month (17)	7	10	SOF/LDV ±RBV SOF/VEL	Nationwide HCV elimination program; mostly in hospital outpatient clinics	None	Former PWID and people who have never injected drugs
Grebely 2016 Multi- country ³⁵	Post-hoc of three RCTs	-	-	11	4	SOF/LDV ±RBV	Clinical trial	None	Non-OST recipients in the same trial [‡]
Grebely 2016a Multi- country ³⁷	Post-hoc of three RCTs	-	-	21	5	SOF/VEL	Clinical trial	None	Non-OST recipients in the same trial [‡]

Grebelly 2017 Multi-country ³⁶	Pooled data from phase II and III clinical trials	-	-	12	7	GLE/PIB	Clinical trial	None	None
Grebelly 2017a/18 Multi-country ³⁴	Single-arm clinical trial (>1)	Injecting within the past 6 months (100)	Injecting within the past month (74)	9	57	SOF/VEL	Clinical trial; treatment in community or hospital clinics	None	2° definition subgroup compared to all other participants; OST recipients compared to 1° definition
Grebelly 2017b Multi-country ⁴⁰	Post-hoc of phase III clinical trials	-	-	NR		SOF/VEL/VOX † regimen extracted	Clinical trial	None	Non-OST recipients in the same trial [‡]
Lalezari 2015 USA ⁴¹	Phase II, open-label, single-arm trial	-	-	0	100	PrOD+RBV	Clinical trial	None	None
Losikoff 2017 USA ⁴⁷	OC	-	-	4	100	EBR/GRZ SOF/DCV SOF/LDV SOF/VEL	Addiction clinic	None	None
Mazhnaya * 2017 Ukraine ²²	RC& PC (19)	Injecting within the past month (9)	-	26	14	SOF/DCV+RBV SOF+RBV	Community-based clinics	Social support with case management	1° definition compared to OST; OST compared to current and former PWID, and non-PWID with other hepatitis C risk factors
Midgard# 2017/18 Norway	PC (1)	Injecting within the past 6 months (100)	-	N/A	78	N/A	Low-threshold clinic for PWID	N/A	N/A
Morris 2017 Australia ²⁴	Cohort (4)	Injecting within the past year (50)	-	NR	38	SOF/DCV ±RBV SOF/LDV PrO±RBV	Alcohol and other drug addiction clinic	Phone calls, case management, face-to-face meetings	1° definition compared to non-recent PWID at same addiction clinics; OST compared to non-OST recipients (i.e. current PWID, drug counselling or rehabilitation clients)
Puoti 2014 Not-specified ⁴²	Post-hoc of phase II and III trials	-	-	NR	100	PrOD±RBV	Clinical trial	None	None

Read 2017 Australia ²⁵	Cohort (1)	Injecting within the past 6 months (75)	Injecting within the past month (68)	10	25	SOF/LDV SOF/DCV PrOD±RBV	Community-based clinic for PWID	As needed DOT, phone follow-up, medication delivery to prisons, police cells and hospital wards	1° definition compared to former PWID only; OST compared to non-OST recipients (current and former PWID)
Rockstroh 2017 Multi-country ⁴⁵	PC (100)	-	-	95	25	SOF/DCV ±RBV	European Union wide compassionate use program for DCV	None	Participants in the same compassionate use program for DCV
Saeed* 2017 Canada ²⁶	PC (18)	Injecting within the past 6 months (19)	-	NR	NR	SOF/DCV SOF/LDV SOF/RBV SOF/SMV ±RBV PrO±RBV	Hospital and community	None	Former PWID and people who have never injected drugs
Schutz 2018 Austria ²⁷	Open-label, non-interventional proof-of-concept study (1)	Injecting within the past 6 months (58)	-	0	100	SOF/LDV	Low threshold harm reduction centre	Daily DOT with intensive case-management. Treatment course extended if doses missed –such that all received 56 doses.	1° definition compared to former PWID
Tait 2017 Scotland ⁴³	OC	-	-	32	50	All-oral DAAs not further specified	Hospital clinic with medication dispensed by community pharmacy	Daily DAA dispensing at community pharmacy for OST recipients	People receiving DAA treatment through a community pharmacy
Valente 2017 Portugal ⁴⁸	Chart review	-	-	20	100	PrOD SOF/LDV SOF+RBV	Hospital-based	None	None

*Additional data or information not included in the primary citation provided by author

† This paper also included participants treated with SOF/VEL, however outcomes for this treatment group were already extracted in Grebely 2016a

‡ People reporting 'clinically significant' substance use in the past year and/or those with a positive urine drug screen (for non-cannabinoids) were excluded from these trials

Paper reports reinfection only

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; ITT, intention-to-treat; LDV, ledipasvir; mITT, modified intention-to-treat; NR, not reported; OC, observational cohort; OST, opioid substitution therapy; PC, prospective cohort; PrO, paritaprevir/ritonavir/ombitasvir; PrOD, paritaprevir/ritonavir/ombitasvir plus dasabuvir; PWID, people who inject drugs; RBV, ribavirin; RC, retrospective cohort; RCT, randomised controlled trial; SOF, sofosbuvir; SMV, simeprevir; VEL, velpatasvir; VOX: voxilaprevir.

Table 3: Studies that report reinfection in recent PWID and/or OST recipients

First Author Year	Reinfection definition	Recent PWID			OST recipients		
		Reinfection % (n/N)	Follow up duration (PY)	Rate per 100 PY [95% CI] [#]	Reinfection % (n/N)	Follow up duration (PY)	Rate per 100 PY [95% CI] [#]
Bouscaillou 2017 ^{17,52 †}	Recurrence after SVR12 through to 9 – 15 months after EoTR	0.6 (1/169) <i>and</i> * 0.6 (1/156)	162.5	1.2 [0.1 - 4.4]	-	-	-
Conway 2016 ¹⁸	Recurrence 3 – 12 months after SVR12	0 (0/32)	32	0.0 [0.0 - 0.1]	-	-	-
Conway 2017 ^{† 34,55}	Recurrence between SVR12 – SVR24 (phylogenetic analysis)	2.8 (1/36)	NR	-	-	-	-
Dore 2016 ^{† 38,56}	Recurrence between EoTR through to up to 36 months of follow up (viral sequencing)	-	-	-	2.0 (6/296) <i>and</i> ** 2.0 (4/199)	426	2.3 [1.1 – 4.3]
Eckhardt 2018 ¹⁹	Recurrence between SVR12 – SVR24 (+change in genotype)	4.1 (2/50)	NR	-	-	-	-
Grebely 2016 ³⁵	Recurrence 4-24 weeks after EoTR (deep sequencing)	-	-	-	0 (0/66)	1822	0.0 [0.0 – 0.2]
Grebely 2016a ³⁷	Recurrence 4-24 weeks after EoTR (deep sequencing)	-	-	-	0 (0/51)	NR	-
Grebely 2017a/18 ³⁴	Recurrence between EoTR and SVR24 (viral sequencing)	1.0 (1/97)	38	2.6 [0.1 - 14.7]	-	-	-
Midgard 2017 ^{† 51,57}	Recurrence after EoTR (monitoring every 3 months after treatment; viral sequencing)	2.4 (2/83)	71	2.8 [0.3 - 10.2]	-	-	-
Schutz 2018 ²⁷	Recurrence between SVR12 and SVR24 (change in subtype/genotype)	4.3 (1/23)	5.3	18.9 [0.5 - 105.1]	5 (2/40)	9	22.2 [2.7-80.3]

Exact 95% Poisson confidence interval

† Reinfection data from a subsequent publication and/or author contact

*This study had two follow up periods; 169 participants were followed for 9 months after EoTR, of whom 156 were followed for an additional period.

** This study had two follow up periods, 296 participants received 24 weeks of follow up. Of these, 199 were followed for an additional period

Abbreviations: EoTR, end of treatment response; NR, not reported; OST, opioid substitution therapy; PWID, people who inject drugs; PY, person years; SVR12, sustained viral response 12 weeks after end of treatment

Table 4: Studies that report adherence

Author, Year	Adherence intervention	Adherence definition	Measurement method	Adherence recent PWID % (n/N)	Adherence OST % (n/N)	Adherence non-OST group % (n/N)
<i>Community-based</i>						
Schutz 2018 ²⁷	Daily directly observed therapy with intensive case-management. Treatment course extended if doses missed, such that all received 56 doses.	Not defined, however all participants missed ≤1 dose throughout the study	Directly-observed therapy	100 (23/23*)	100 (40/40 [†])	-
<i>Clinical trials</i>						
Dore 2016 ³⁸	None	>95% of doses taken	Participants provided with electronic medication diary	-	96 (283/294)	-
Grebely 2016 ³⁵	None	≥80% of doses taken	Pill count at weeks 4, 8, ±12	-	93 (65/70)	92 (1737/1882)
Grebely 2016a ³⁷	None	≥90% of doses taken	Pill count at all study visits	-	90 (46/51)	96 (946/984)
Grebely 2017 ³⁶	None	≥90% of doses taken	Pill count (participants with missing data excluded)	-	98 (121/123)	99 (1884/1905)
Grebely 2017a/18 ³⁴	None	≥90% of doses taken	Electronic blister pack that recorded time and date that each dose was accessed	66 (68/103)	-	-

Abbreviations: OST, opioid substitution therapy; PWID, people who inject drugs

*All recent PWID were on OST

[†]Includes 23/23 of recent PWID group (all study participants were on OST)

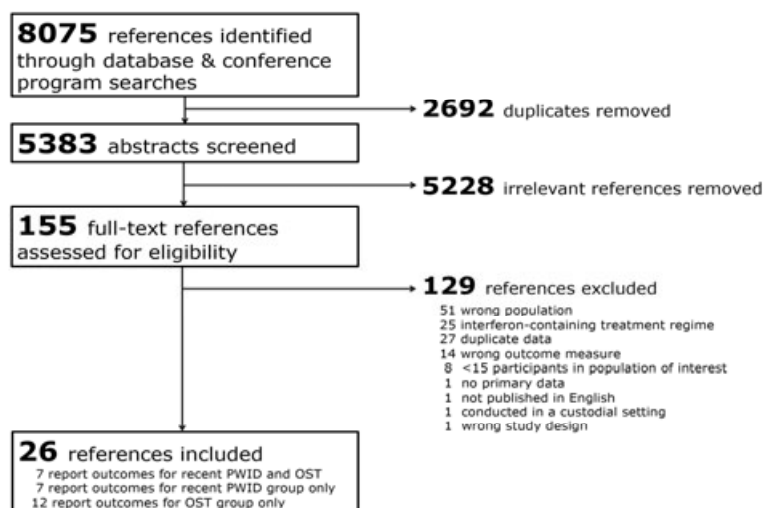


Figure 1: PRISMA diagram detailing study selection results

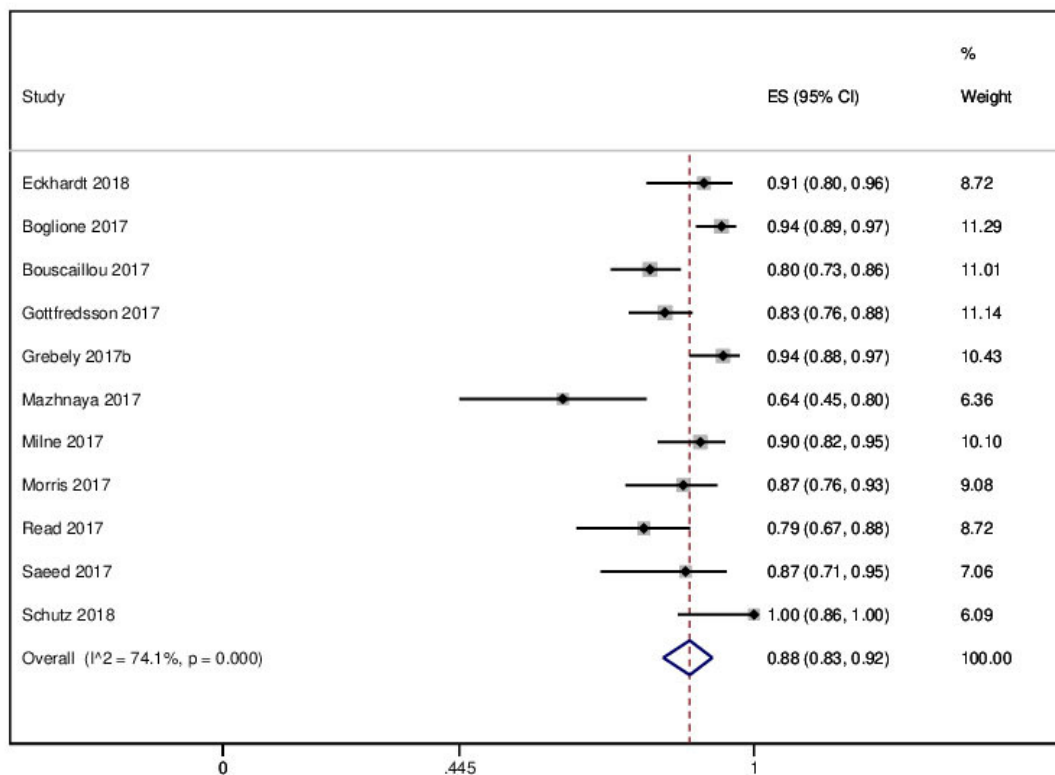


Figure 2:(a) SVR in recent PWID (ITT)

ITT, intention-to-treat analysis; mITT, modified intention-to-treat analysis; OST, opioid substitution therapy; PWID, people who inject drugs; SVR, sustained viral response

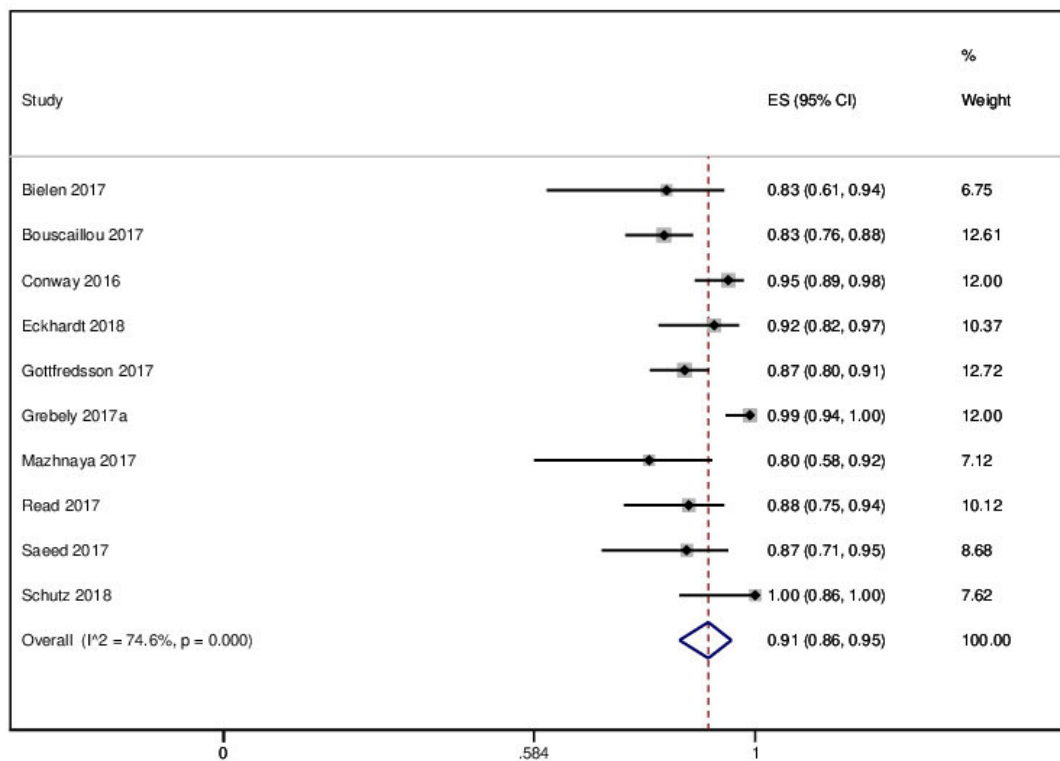


Figure 2:(b) SVR in recent PWID (mITT/as-defined)
 ITT, intention-to-treat analysis; mITT, modified intention-to-treat analysis; OST, opioid substitution therapy;
 PWID, people who inject drugs; SVR, sustained viral response

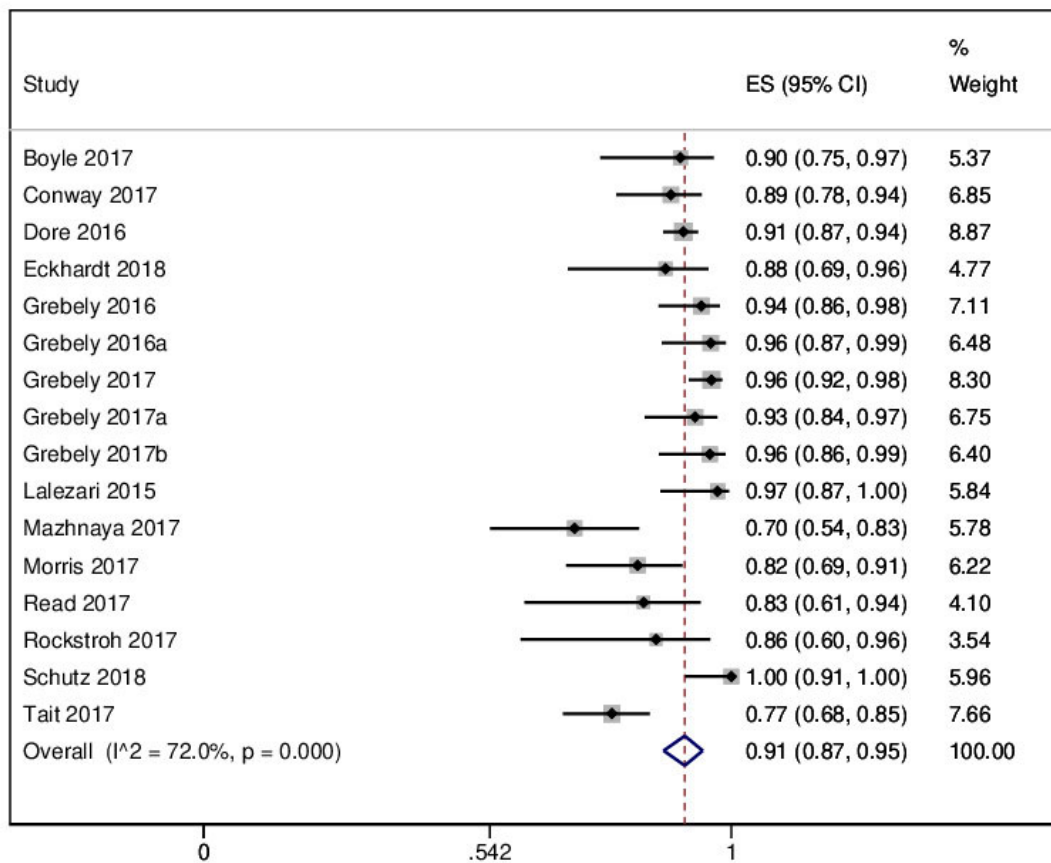


Figure 2:(c) SVR in OST recipients (ITT)

ITT, intention-to-treat analysis; mITT, modified intention-to-treat analysis; OST, opioid substitution therapy; PWID, people who inject drugs; SVR, sustained viral response

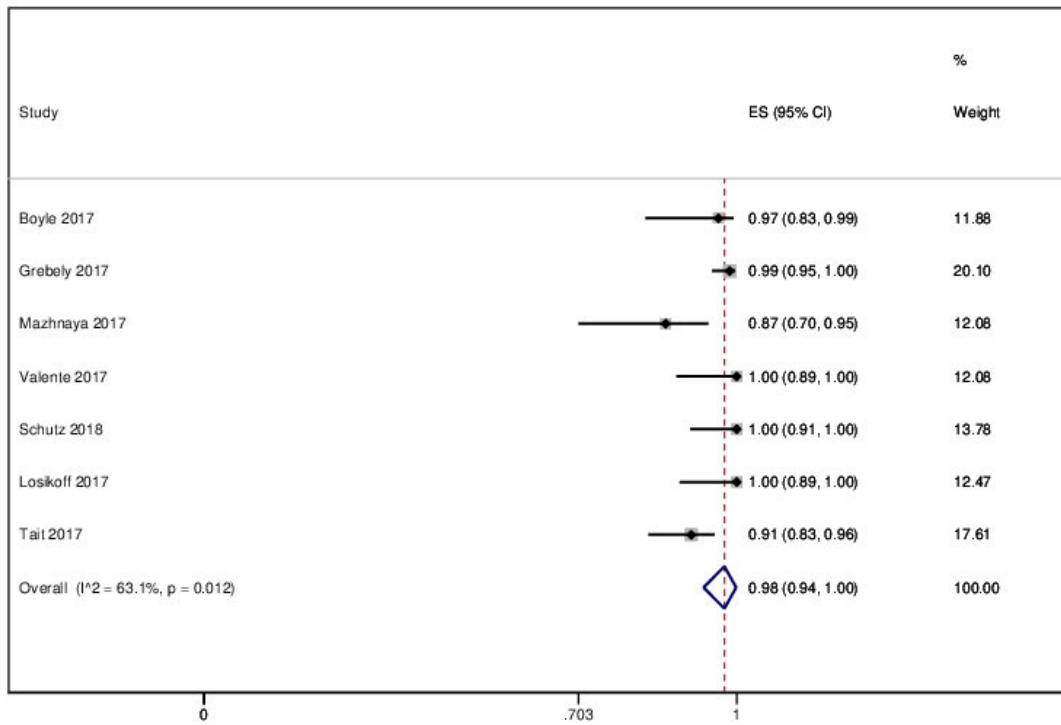


Figure 2:(d) SVR in OST recipients (mITT/as-defined)

ITT, intention-to-treat analysis; mITT, modified intention-to-treat analysis; OST, opioid substitution therapy; PWID, people who inject drugs; SVR, sustained viral response

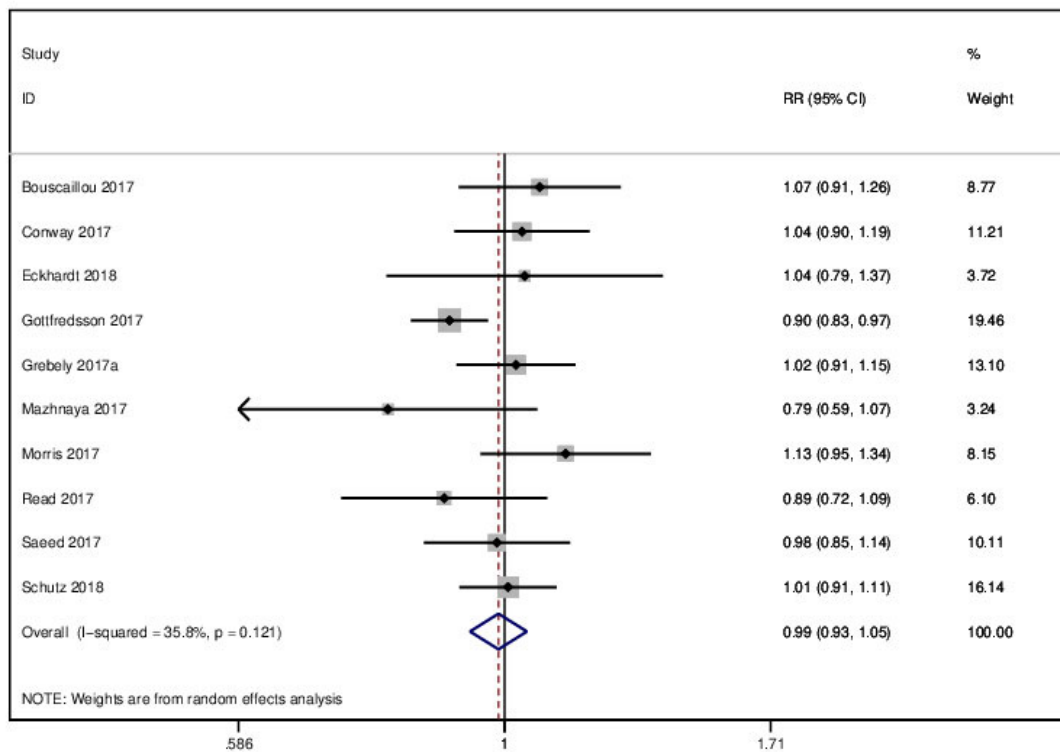


Figure 3:(a) Relative risk of achieving SVR in recent PWID

PWID, people who inject drugs; SVR, sustained viral response

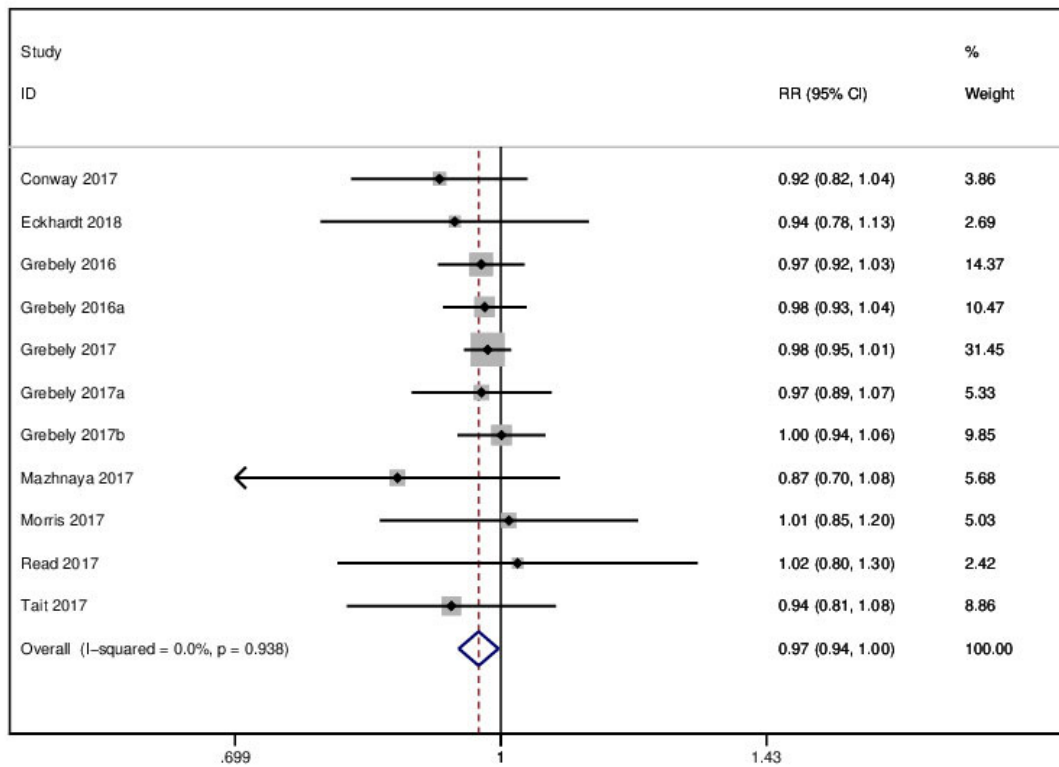


Figure 3:(b) Relative risk of achieving SVR in OST recipients

OST, opioid substitution therapy; SVR, sustained viral response